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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,669	11/01/2001	Robert H. Broyles	OKL010-107/00727A	5327

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EXAMINER	
QIAN, JANICE LI	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/003,669	BROYLES ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,19,22 and 24-27* is/are pending in the application.

4a) Of the above claim(s) *11 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,19,22,24,25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

The amendment and response filed 10/20/03 have been entered. Claims 3, 12, 13 have been canceled. Claims 1, 11, 19, 22 have been amended. Claims 24-27 are newly submitted.

It is noted that the amended claim 11 and new claim 26 are drawn to a non-elected invention (groups II and V respectively, see paper #10), therefore, are withdrawn from consideration in this application.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 10/23/03 response would be addressed to the extent that they apply to current rejection.

Specification

The computer readable form of sequence listing submitted 10/20/03 is technically flawed, thus, could not be entered into the PTO database. A full response to this Office action must include a new CRF Sequence Listing and a statement that the content of the paper and CRF copies are the same.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 19, and 22 stand rejected and claims 24, 25, and 27 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The previous rejection has been modified in view of the claim amendment.

Applicants argue that "the derivative thereof" has been replaced with "conservatively modified variants thereof", which is an accepted term by MPEP §2422.03, 7th paragraph.

The argument has been fully considered but found not persuasive because first, it is noted that claim 22 has not been amended as indicated. Second, the indicated MPEP section discusses issues in sequence listing, not a guidance for examination with respect to written description requirement under 35 U.S.C. § 112, 1st paragraph. Whether such requirement is met for each application is reviewed on a case-by-case basis. In the instant case, the specification fails to teach the *conservatively modified variants* of ferritin H. Turning to the state of the art, *Welch et al* (Free Radic Biol Med 2002;33:399-408) teach at a post-filing date that the cysteine at position 90 is essential for the formation of ferritin aggregates during iron loading. Such knowledge is not known at the time of instant effective filing date, and fails to be disclosed by the specification. Therefore, the specification does not provide an adequate written description of the claimed invention in such a way as to reasonably convey to one skilled in the relevant

art that the inventors, at the time the application was filed, had possession of the claimed invention.

To the extent that the claimed methods and composition are not adequately described in the instant disclosure, claims 1, 19, 22 stand rejected and claims 24, 25, 27 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been adequately described for reasons of record and set forth foregoing.

Claims 1, 19, and 22 stand rejected and claims 24, 25, and 27 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue that claims now are all drawn to treating sickle cell disease, the specification teaches depressing beta globin production by expressing ferritin-H, and the prior art discloses a variety of methods of transforming cells to incorporate foreign genes. The arguments are not persuasive because the elected invention is exposing globin-producing cells to a ferritin-H protein, not a nucleic acid expressing ferritin-H.

With respect to the differences between in vitro and in vivo data, Applicants argue that ferritin-H effects intracellularly, and the major difference between cells ex vivo and in vivo lie in the reproductive pathways, such differences do not pose the same uncertainties when studying iron management compared to genetic differences in cancer research. The arguments have been fully considered but they are not persuasive. This is because the state of the prior and post-filing art of record as cited clearly indicate that the ex vivo findings in regulating beta globin gene have not fully developed to *in vivo* therapeutic regimen. Although prior art reported that overexpression of ferritin-H downregulates the synthesis of the endogenous ferritin (*Picard et al*), such transient effect has not been shown to be sufficient to change the phenotype of diseased cells, and the specification fails to disclose otherwise. *Mankad* clearly teaches, after instant effective filing date, that the understanding to beta globin gene has not translated to clinically effective therapeutic strategy. Such teaching has clearly shown the difficulties in iron management study is as difficult as the cancer research if not more, that molecular understanding has not translated to clinical benefit yet.

Applicants are again reminded that the ex vivo condition is a simplified model for cellular biochemistry, not only because of the reproductive pathways but because the *in vivo* condition involves interactions of multiple intra- and extra cellular elements, ferritin-H acts not only intracellularly, but also in a nuclear location. As cited in the previous Office action, prior art and the instant specification only teach successful delivery of ferritin-H to nucleus via a nucleic acid expression vector, but are silent with respect to

deliver the ferritin-H protein to the cell nucleus, neither *in vivo* nor *ex vivo*. thus, the scope of the support in the specification (a cell culture assay for an expression vector) does not correlate with the scope of the claims (a method of in vivo treatment with a protein). 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970).

Based on the foregoing discussion, it is apparent that the skilled in the art recognize the intracellular effect of delivering exogenous ferritin-H to iron distribution and metabolism *in vitro* but has not been able to translate such *ex vivo* finding into clinical benefit, and the delivery of ferritin-H was only practiced with the delivery of a *nucleic acid* expressing ferritin-H ex vivo to cultivated cells. In addition to nucleus targeting, protein pharmacokinetics, host immune response would be other concerns for the claimed ferritin-H protein therapy. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for the claimed invention. However, the teachings and guidance present in the specification, as a whole, represent an initial investigation into the feasibility of the development of a useful means for executing ferritin-H therapy, which awaits further development to the practical level.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *in vivo* protein therapy at clinical effective levels, in particular for the treatment of sickle cell diseases, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to

therapeutic regimens with a protein ferritin-H, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The prior rejection of claims 1, 11, 12, and 19 under 35 U.S.C. 102(b) as being anticipated by *Adams et al* (New Eng J Med 1998;39:5-11), and as evidenced by *Atkinson et al* (Biochem Cell Biol 1989;67:52-7, IDS) and *Sowemimo-Coker* (Transfus Med Rev 2002 Jan;16:46-60) is withdrawn in light of the response indicating the ferritin-L, but not ferritin-H, is present in the transfusion.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

QJL